Leukoencephalopathy with Calcifications and Cysts: A Purely Neurological Disorder Distinct from Coats Plus

John H. Livingston[1] Josephine Mayer[2] Emma Jenkinson[2] Paul Kasher[2] Stavros Stivaros[3] Andrea Berger[4] Duccio M. Cordelli[5] Patrick Ferreira[6] Rosalind Jefferson[7] Georg Kutschke[8] Staffan Lundberg[9] Katrin Ounap[10] Prab Prabhakar[11] Calvin Soh[12] Helen Stewart[13] Jon Stone[14] Marjo S. van der Knaap[15] Hilda van Esch[16] Christine van Mol[16] Emma Wakeling[17] Andrea Whitney[18] Gillian I. Rice[1] Yanick J. Crow[1]

[1] Department of Paediatric Neurology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
[2] Department of Genetic Medicine, University of Manchester, Manchester Academic Health Science Centre, Central Manchester Foundation Trust University Hospitals, Manchester, United Kingdom
[3] Imaging, Genomics and Proteomics Research Group, University of Manchester, Manchester, United Kingdom
[4] Department of Pediatric Neurology, Children's Hospital, Harlaching, Munich and University of Mainz, Germany
[5] Child Neuropsychiatry Unit, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy
[6] Division of Medical Genetics, Alberta Children's Hospital, Calgary, Canada
[7] Department of Paediatrics, Royal Berkshire Hospital, Reading, United Kingdom
[8] Department of Pediatrics and Neonatology, Universitätsklinikum des Saarlandes, Homburg, Germany
[9] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
[10] Department of Genetics, Tartu University Hospital, Tartu, Estonia
[11] Department of Neurology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom
[12] Department of Neuroradiology, Salford Royal NHS Foundation Trust, Salford, United Kingdom
[13] Department of Clinical Genetics, Oxford Radcliffe Hospitals NHS Trust, Oxford, United Kingdom
[14] Department of Clinical Neurosciences, Western General Hospital, Edinburgh, United Kingdom
[15] Department of Child Neurology, VU University Medical Center, Amsterdam, The Netherlands
[16] Center for Human Genetics, University Hospitals Leuven, KU Leuven, Leuven, Belgium
[17] North West Thames Regional Genetics Service, North West London Hospitals NHS Trust, Harrow, United Kingdom
[18] Department of Paediatric Neurology, Southampton General Hospital, Southampton, United Kingdom

Address for correspondence John H. Livingston, MBCHB, Department of Paediatric Neurology, F Floor Martin Wing, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom (e-mail: jh.livingston@leedsth.nhs.uk).

Neuropediatrics

received
September 12, 2013
accepted after revision
November 13, 2013

DOI http://dx.doi.org/10.1055/s-0033-1364180.
ISSN 0174-304X.

Abstract

Objective With the identification of mutations in the conserved telomere maintenance component 1 (*CTC1*) gene as the cause of Coats plus (CP) disease, it has become evident that leukoencephalopathy with calcifications and cysts (LCC) is a distinct genetic entity.

Patients and Methods A total of 15 patients with LCC were identified from our database of patients with intracranial calcification. The clinical and radiological features are described.

Results The median age (range) at presentation was 10 months (range, 2 days–54 years). Of the 15 patients, 9 presented with epileptic seizures, 5 with motor abnormalities, and 1 with developmental delay. Motor abnormalities developed in 14 patients and cognitive problems in 13 patients. Dense calcification occurred in the basal ganglia, thalami, dentate nucleus, brain stem, deep gyri, deep white matter, and in a pericystic distribution. Diffuse leukoencephalopathy was present in all patients, and it was usually symmetrical involving periventricular, deep, and sometimes subcortical, regions. Cysts developed in the basal ganglia, thalamus, deep white matter, cerebellum, or brain stem. In unaffected areas, normal myelination was present. No patient demonstrated cerebral atrophy.

Conclusion LCC shares the neuroradiological features of CP. However, LCC is a purely neurological disorder distinguished genetically by the absence of mutations in *CTC1*. The molecular cause(s) of LCC has (have) not yet been determined.

Keywords

- intracranial calcification
- leukoencephalopathy
- coats plus

Introduction

In 1988, Tolmie et al[1] described two female siblings demonstrating the association of a bilateral exudative retinopathy, Coats disease, with intracranial calcification. These sisters also had sparse hair, dystrophic nails, and slow prenatal and postnatal growth. Subsequent follow-up detailed the development of ataxia, dystonia, skeletal abnormalities including osteopenia with resulting fractures, gastrointestinal vascular abnormalities, and liver disease.[2,3] The disorder was designated as CP syndrome.

In 1996, Labrune et al[4] reported three children with a progressive mixed neurological disorder associated with leukoencephalopathy, intracranial calcifications, and enlarging brain cysts (LCC). No eye, bone, or gut abnormalities were described. Subsequently, similar individuals with retinal telangiectasias, brain calcification, and cysts were reported by Nagae-Poetscher et al[5] and Linnankivi et al,[6] and who were thought to represent an overlap between CP and LCC. These observations led to the hypothesis that the two disorders were part of the same spectrum termed cerebroretinal microangiopathy with calcifications and cysts (CRMCC).[3,6] The presence of affected siblings indicated that CRMCC was probably an autosomal recessive disorder, although the molecular basis of the phenotype was unknown.

We recently showed that mutations in *CTC1*, encoding conserved telomere maintenance component 1, cause Coats plus, a multisystem disorder the most characteristic features of which are as follows: retinal telangiectasia and exudates (Coats disease), intracranial calcification with an associated leukoencephalopathy and brain cysts, osteopenia with a tendency to fractures and poor bone healing, and a high risk of life-limiting gastrointestinal bleeding and portal hypertension caused by the development of vascular ectasias in the stomach, small intestine, and liver.[7] Mutations in *CTC1* were not identified in any patient with a purely neurological disorder, indicating that LCC and CP are distinct entities. Polvi et al[8] also reported *CTC1* mutations in 11 patients with what they describe as CRMCC. All of the patients had extraneurological features. In 10 patients there was retinal involvement, and in the remaining patient osteopenia and fractures. Again, they concluded that *CTC1* mutations were not responsible for the LCC phenotype. Here, we have reviewed the clinical and radiological features of 15 patients with LCC.

Patients and Methods

The medical records of patients with available neuroradiological data were reviewed. The inclusion criteria for the study were as follows: (1) Imaging demonstrating (a) leukoencephalopathy; (b) characteristic intracranial calcification as described previously[2,3,6,9]; (c) intraparenchymal brain cysts. (2) Absence of (typical) extraneurological clinical features of CP syndrome, specifically: eye, bone, gastrointestinal, hepatic, and skin pathology. (3) Absence of mutations in *CTC1*.

Computed tomographic (CT) and magnetic resonance (MR) images were reviewed by the authors and their features scored using a scoring system devised for the study of intracranial calcification.[9] CT and MR data were scored separately.

Results

Clinical Features

A total of 15 patients from 12 families, including 3 sibling pairs were identified. A history of consanguinity was present in only one patient (patient 12) whose parents were second cousins (►**Table 1**).

Birth History and Presenting Features

Four patients had intrauterine growth retardation. One patient was noted to be microcephalic at birth, but had an appropriate birth weight. The median (range) age at presentation was 18 months (range, 2 days–54 years). The most common presenting features were focal or generalized epileptic seizures or a motor disorder including; tremor, hemiparesis, gait abnormality, head tilt, and motor delay. One patient presented with global developmental delay.

Neurological Symptoms

All but one patient has developed a mixed neurological picture. Asymmetrical pyramidal signs, seizures, dysarthria, ataxia, and dystonia were commonly described. Cognitive impairment was common and was severe in four patients. Slow cognitive deterioration following normal neurodevelopment was noted in five patients, starting from the ages of 1 to 9 years. Nine patients underwent surgical intervention for drainage of brain cysts. Ommaya reservoirs were inserted at the age of 14 months in patient 5, and at the age of 10 years in patient 12. Hydrocephalus was treated with a ventriculoperitoneal shunt in patient 8. At the time of writing, two patients have died. Patient 11, the oldest patient in this series, died at the age of 59 years following gradual neurological deterioration over several months. Patient 12 died at the age of 15 years after several neurosurgical procedures for recurrent cyst development.

The clinical course within sibships is very similar even though different complications may occur at different ages, for example, patient 5 developed an acute hemiparesis at the age of 5 years, whereas her older sister had only a mild hemiparesis.

Table 1 Clinical features of patients

Neonatal history	
Preterm	3
IUGR	4
Microcephaly	1
Median (range) age at presentation (mo)	18 (0.5–648)
Affected sibling	3
Presenting feature	
Epileptic seizures	9
Motor disorder	4
Developmental delay	2
Median (range) age at most recent follow-up (y)[a]	12 (5–59)
Clinical features	
Epilepsy	9
Cognitive impairment	13 (severe in 4)
Motor disorder	14
Hemiparesis	5
Dystonia	5
Neurosurgical treatment[b]	9
Neuropathological study	4

Abbreviation: IUGR, intrauterine growth restriction.
[a]Two patients died at the age of 15 and 59 years, respectively.
[b]Drainage of cyst in six, ventriculoperitoneal in one, or cystoperitoneal shunt in one.

Radiological Features

No patient demonstrated cerebral or cerebellar atrophy (►**Table 2**).

Table 2 Radiological features of 15 patients with LCC summarizing both CT and MR findings

Leukoencephalopathy	
Symmetrical	13
Periventricular	15
Deep	15
Subcortical[a]	10
Cerebellar	7
PLIC	8
Contrast enhancement	9/10
Swelling of brain stem	5
Calcification	
Basal ganglia	15
Thalami	15
Dentate	5
Cerebellar white matter or cortex	5
Brain stem	7
Cortical	11
Cerebral white matter	10
Pericystic	8
Cysts[b]	
More than 5	6
2–5	3
Single	4
Location of cysts	
Basal ganglia/thalami	5
Hemispheric white matter	11
Brain stem	4
Cerebellum	2

Abbreviations: CT, computed tomography; LCC, leukoencephalopathy with calcifications and cysts; MR, magnetic resonance; PLIC, posterior limb of internal capsule.
[a]In 8/10, subcortical involvement was patchy.
[b]Two patients did not have cysts but had affected siblings with typical appearances.

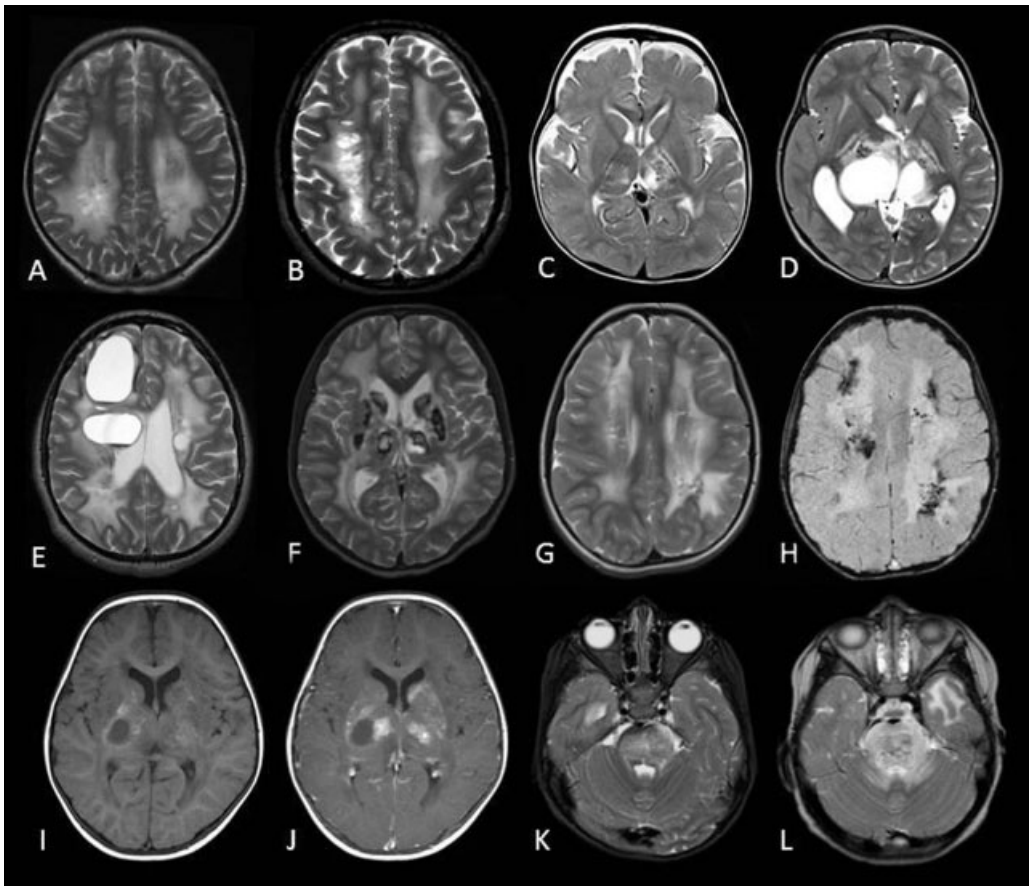

Fig. 1 Magnetic resonance features of leukoencephalopathy with calcifications and cysts A–G, K, and L are T2-axial images; H is a susceptibility-weighted image (SWI); I and J are T1-axial images precontrast (I) and postcontrast (J) enhancement. (A) Patient 4 aged 14 years and (B) patient 6 aged 18 years demonstrating confluent high signal in deep white matter with subcortical sparing and multiple small cysts within abnormal white matter. Note the posterior predominance in A. Bilateral thalamic cyst development is illustrated in patient 13 at (C) 10 months and (D) 3 years. There is also involvement of the posterior limb of the internal capsule even in the early scan. (E) The typical leukoencephalopathy with large space-occupying cysts within the centrum semiovale is demonstrated in patient 10 aged 26 years. (F) Rock-like basal ganglia and thalamic calcification has mixed signal characteristics with areas of abnormal low signal and abnormal high signal in this patient aged 14 years. Calcification may not always be apparent on T2 images as shown in G. Compare this with the SWI from the same study (H) demonstrating several low-signal areas within the hemispheric white matter representing calcification. Gadolinium contrast enhancement occurs within the calcified areas as demonstrated in these precontrast (I) and postcontrast (J) T1 image from patient 5 aged 19 months. Two examples of swelling and high signal of the pons are shown, (K) patient 13 aged 3 years and (L) patient 8 aged 2 years.

Magnetic Resonance Features

The leukoencephalopathy was apparent as confluent high signal on T2-weighted and fluid-attenuated inversion recovery images involving the periventricular and deep hemispheric white matter, often, but not always, sparing the subcortical white matter (►**Fig. 1A, B, E–G**). This was symmetrical in all but two patients. In one patient, there was a marked posterior-to-anterior gradient with relative sparing of the frontal lobes (►**Fig. 1A**). Eight patients had involvement of cerebellar white matter.

Serial MR imaging was available in nine patients. Patients 14 and 15 (siblings) both had normal neonatal MR images. By the age of 18 months in patient 15, and 8 years in patient 14, widespread leukoencephalopathy and calcification were apparent. Patient 8 had a normal MR at the age of 2 months but had developed the full triad of appearances (leukoencephalopathy, calcification, and cysts) by the age of 2.5 years. The earliest age by which the full triad of features was seen was 10 months (patient 13).

The leukoencephalopathy was initially progressive in all patients with serial scans. However, in three of six patients with more than two MR scans, the leukoencephalopathy has apparently remained stable over many years.

Computed Tomographic Features

On CT, the calcification was marked and, in the seven patients with serial scans, usually progressive. The earliest CT was at the age of 2 weeks demonstrating subtle white matter and basal ganglia calcification. Blush-like calcification of the basal ganglia, thalami, and deep white matter (►**Fig. 2G**) was present in two further patients scanned at 2 and 6 months, respectively. All patients eventually demonstrated dense rock-like calcification involving the deep gray matter. Usually, this involved the globus pallidus, putamen, caudate, and thalamus (►**Fig. 2D, H**). Dentate

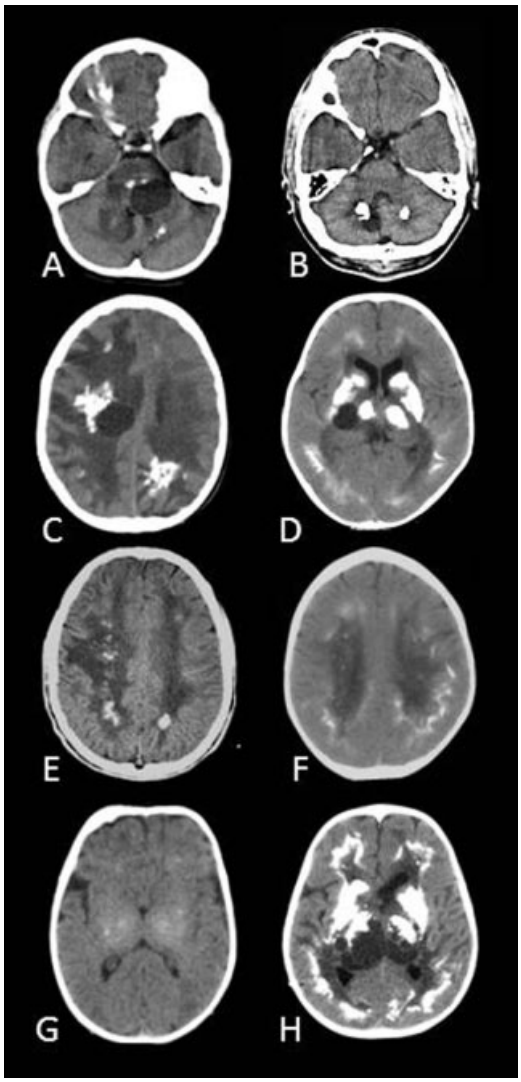

Fig. 2 Computed tomographic (CT) features of leukoencephalopathy with calcifications and cysts. Rock-like calcification of the basal ganglia and thalami (D, H) and the dentate nucleus (A, B) is characteristic. In addition, there is usually deep cortical calcification which is often continuous (D, F, H). (E, F) Calcification may also occur in the deep white matter and (C) around the cysts. Serial scans performed at (G) 2 months and (H) 5 years demonstrate progression of calcification. At 2 months, there is only a blush of calcification in the basal ganglia whereas the full radiological spectrum is apparent by 5 years. The cysts and abnormal low-attenuation white matter are also readily apparent on CT images.

nucleus calcification (►**Fig. 2A, B**) and brain stem calcification (►**Fig. 2A**) was present in seven patients. Cortical calcification was also characteristic. Most commonly, calcification was seen in the depths of the cortical gyri, and sometimes ran as a continuous serpiginous line of calcification following the white–gray junction (►**Fig. 2D, F, H**). Some patients had dense gyriform calcification involving the superficial and deep cortex.

Although the calcification predominantly involves gray matter, spot or blush-like calcification was seen in the deep frontal, parietal, or temporal white matter (►**Fig. 2E, F**). Calcification was also seen around cysts, or in the cyst wall (►**Fig. 2C**).

Although CT scanning is more sensitive for the detection of calcification than MR, calcification was apparent on MR imaging in all patients.

Cysts were present in 13 patients. We have included two patients who do not have cysts at the time of writing. Both of these patients had affected siblings who demonstrated the full radiological phenotype. Cysts could be single, or multiple, with six patients having more than five cysts. Cysts developed in many different locations, including: cerebellar white matter, brain stem, basal ganglia and thalami, deep hemispheric white matter, and intraventricular (►**Figs. 1D, E, I** and **2A–D, H**). In several patients, cysts appeared to develop from the dorsal thalamic region. In four patients with serial scans, cysts were not present on the first images but developed later.

Contrast enhancement was seen in 9 of the 10 patients to whom it was given (►**Fig. 1I, J**). Enhancement was typically seen around the cysts or in the basal ganglia in areas of dense calcification. A further feature, seen in five patients, was diffuse swelling and high signal on T2 sequences in the brain stem, especially the pons (►**Fig. 1K, L**).

Pathology

In four patients, biopsy material was available. Patient 3 demonstrated gliotic white matter, ectatic, sinusoidal vessels with thin walls surrounded by hyaline tissue with hemosiderin and calcification. Cerebral tissue from patient 10 demonstrated gliosis with flecks of calcification within the affected white matter. Patient 12 had drainage of a cyst and biopsy. This demonstrated cystic spaces of various size and abnormal white matter with reactive gliosis and almost complete demyelination. Patient 13 had a cyst wall biopsy which demonstrated gliosis and calcifications, Rosenthal fibers, and the presence of hyaline deposits within blood vessel walls.

Discussion

Despite the remarkable similarity of the neuroradiological phenotype, we have recently demonstrated that the patients described here are genetically distinct from patients with Coats plus. We therefore propose to refer to the phenotype as LCC, and differentiate this phenotype from CP on the basis of an absence of mutations in *CTC1* and the extraneurological features seen in the latter disorder.[7] In the absence of an identified molecular cause, the current diagnostic criteria for LCC should include all three radiological features, namely, leukoencephalopathy, calcification, and cysts. However, we note that in this series, six patients had early scans that did not show cysts. We are also aware of other patients with leukoencephalopathy and calcification (but no cysts), whose scans are apparently otherwise identical with LCC patients. At present, it is not known whether cyst development is a universal feature of this disorder.

The genetic basis of LCC remains unclear at this time, although the presence of three (female) sibling pairs in our cohort suggests that LCC is inherited as an autosomal recessive trait in at least some families. Of note, our ongoing genetic studies indicate that the condition may be genetically

Table 3 Clinical and pathological features of published cases of LCC

	Number of patients	Age at presentation	Age at time of report	Low birth weight	Presenting features	Seizures	Motor signs	Cognitive decline	Extra neurological features	Neurosurgical intervention	Pathology
Pediatric presenting											
Labrune et al[4]	3	4–11 y	6–15 y	–	Seizures (2), ataxia	3	3	3	Multiple café au lait spots in 1	2	Angiomatous changes, microcalcifications, Rosenthal fibers
Nagae-Poetscher et al[5]	2	Birth–2 y	9,14 y	–	Hemiplegia, seizures and microcephaly	1	2	1	–	1	Fibroglial tissue, Rosenthal fibers, microcalcifications
Brenner et al[10]	1	1 mo	20 y	–	Seizures	Y	Y	1	–	N	–
Linnankivi et al[6]	1	14 y	Died at the age of 43 y	–	Seizures, spasticity	Y	A,S	1	–	Y	Gliosis, thickened small vessel wall
Briggs et al[3]	2	3 mo and 8 y	3 y and 26 y	1	Motor delay, hemiparesis	N	A,D,S	NA	–	–	–
Marelli et al[11]	1	12 y	45 y	–	Seizures	Y	A,S	N	–	Y	Dilated thick walled vessels, angiomatous-like. microcalcifications
Osman et al[12]	1	2 y	42 y	N	Diplegia	Y	S,D	N	–	N	–
Adult presenting											
Berry-Candelario et al[13]	1	24 y	27 y	–	Headache, ataxia, diplopia	N	A	N	–	Y	Cyst wall biopsy only—no abnormalities
Ummer et al[14]	1	50 y	50 y	–	Headache, ataxia	Y in childhood	A,S	N	–	Y	Gliosis, Rosenthal fibers, angiomatous, microhemorrhages and microcalcifications
Gulati et al[15]	1	31 y	36 y	–	Seizures, hemiparesis, tremor	Y	H,S	N	–	N	–
Daglioglu et al[16]	1	26 y		–	Vertigo, vomiting, papilledema	N	N	N	–	Y	Gliosis, calcification of vessels, demyelination
Armstrong et al[17]	1	Possibly infancy. Then 21 y	32 y	N	Seizures	Y	H, dysmetria	Y	Possibly bony involvement	Y	Thick small vessel walls, telangiectatic pattern, perivascular calcification, Rosenthal fibers
Corboy et al[18]	1	44 y	Died at the age of 60 y	–	Headaches, ataxia, seizures	Y	A	Y	–	Y	Angiomatous vessels, fibrinoid necrosis, Rosenthal fibers, microcalcifications
Kaffenberger et al[19]	1	54 y	59 y	–	Urinary urgency, change in behavior, headaches	N	A,D,H	Y	–	Y	Gliosis, Rosenthal fibers, hemosiderin and microcalcifications
Marelli et al[11]	1	27 y	27 y	–	Symptoms of raised intracranial pressure	N	H, ophthalmoplegia	Y mild	–	Y	Angiomatous microangiopathy, thickening of vessel walls, Rosenthal fibers, microcalcifications
Wargon et al[20]	1	30 y	30 y	–	Acute hemiparesis	N	H	N	–	N	–
Sener et al[21]	1	17 y	23 y	–	Seizures	Y	H	–	–	Y	Gliosis, angiomatous changes. Vessel wall thickening. Calcification in vessel walls. Rosenthal fibers

Abbreviations: A, ataxia; D, dystonia; H, hemiparesis; mo, months; N, no; NA, data not available; S, spasticity; Y, yes; y, years.

heterogeneous, a suggestion which might explain the very wide age range seen in our series. Moreover, as for Coats plus, we note a paucity of affected individuals born to consanguineous parents, perhaps suggesting that the combination of a "severe" and "mild" mutation is required to generate the LCC phenotype.

Of the 15 patients, 13 patients presented were younger than 10 years, and 12 of these younger than 5 years when they first developed symptoms and signs of disease. One patient presented as an adult at the age of 54 years. We have included him here because his radiological features were indistinguishable from those of our other cases.

The clinical picture seen in our cohort is consistent with that reported in other published cases[10–21] (►**Table 3**). We consider that there are 20 patients described in the literature with a phenotype definitely consistent with LCC, while in several other articles we believe that the clinical and neuroradiological diagnosis of LCC is less certain. Of these 20 cases, 10 presented as adults. These adult patients are radiologically indistinguishable from patients identified in the pediatric setting, although they were more likely to present with features of raised intracranial pressure due to cyst development, with or without hydrocephalus. In contrast, younger patients most typically have been described to present with other neurological features, even if they later developed pressure-related symptoms associated with cyst development.

Some adult presenting cases[11,17] apparently demonstrated nonprogressive neurological features in childhood, before experiencing symptoms of raised intracranial pressure in adulthood. This is in contrast to five of our patients who developed a progressive disorder in childhood. The youngest case of cyst development in our series occurred at the age of 19 months (patient 5). Furthermore, four patients (patients 4, 8, 13, and 15) had scans at the age of 8 years, 2, 10, and 18 months, respectively, with no cysts, before developing cysts at the age of 12 years, 32, 31, and 62 months, respectively. It is not clear on clinical or radiological criteria whether adult presenting cases constitute a distinct subgroup of LCC.

The leukoencephalopathy seen in LCC is usually, but not always, symmetrical, may have a posterior-to-anterior gradient, involves periventricular and deep white matter, and often, but not always, subcortical white matter. The cerebral hemispheres are primarily involved, but cerebellar white matter is also affected in many (8/13). A notable feature of the LCC (and Coats plus) neuroradiological phenotype is a lack of brain atrophy, and the presence of normal myelination in nonaffected areas, in all cases. This perhaps argues against a primary disorder of white matter.

The pattern of intracranial calcification seen in LCC is characteristic, but not on its own pathognomonic. Calcification predominantly involves the gray matter—both deep nuclei and cortical. Rock-like aggregates in the basal ganglia and thalami were present in all patients. Similar intracranial calcification was seen in the dentate nucleus. This pattern is not specific, being identical to what is often reported in Fahr disease. Cortical calcification, especially involving the depths of the gyri, is also typical, being seen in nine of our patients. Again, this is a feature that has been consistently reported in patients with Fahr disease. In contrast, brain stem calcification is an infrequently reported feature of the latter condition. Although gray matter calcification is predominant, spot calcification in the deep white matter also occurs in LCC, and calcification in cyst walls is common.

Cyst development is the third defining feature of LCC. Radiologically, the cysts are space occupying, and often enlarging, with a ballooned appearance in distinction from nonspace occupying "holes" that may be seen in several other disorders (including other, distinct, conditions demonstrating the combination of intracranial calcification, and leukoencephalopathy, e.g., Aicardi–Goutières syndrome).[9] Cysts can occur in many locations including the brain stem, but they were frequently seen to arise from the posterior thalamus expanding into the lateral ventricles.

There are many disorders where calcification and leukoencephalopathy occur together (►**Table 4**). Most of these can be easily distinguished from LCC on clinical and radiological grounds. Notably, the normal myelination and lack of cerebral atrophy in LCC enables many of these disorders to be excluded.

Pathological data are available from several patients with LCC, which has allowed for analysis of brain and cystic material (►**Table 3**). These data are remarkably consistent. Thus, in the white matter, gliosis, variable degrees of demyelination, and prominent Rosenthal fiber formation, often with

Table 4 Causes of leukoencephalopathy and calcification

LCC
Coats plus
Aicardi–Goutières syndrome
Congenital CMV and other congenital infections
RNASET2 mutation (cystic leukoencephalopathy without megalencephaly)
COL4A1 mutation related disease
Cockayne syndrome
X-linked adrenoleukodystrophy
Krabbe leukodystrophy
Alexander disease
Mitochondrial disease (various)
Cerebrovascular diseases, e.g., Vein of Galen malformation
Vasculitides, e.g., SLE
Hereditary diffuse leukoencephalopathy with spheroids
Nasu–Hakola disease
Cerebrotendinous xanthomatosis
Posthypoxic ischemic injury
Acquired CNS infection
Postradiotherapy

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; LCC, leukoencephalopathy with calcifications and cysts; SLE, systemic lupus erythematosus.

microcalcifications around small vessels, have been consistently described.[4,5,11,14,17–19,21] Small blood vessels are commonly reported as "angiomatous," thick walled, with microcalcifications and microhemorrhages.[4,11,14,17,18,21] It is these consistent pathological findings that have led to the designation of LCC as a "microangiopathy." To our knowledge, there is no difference in the brain pathology seen in patients with LCC and those with Coats plus.[3,6]

In conclusion, we provide data on 15 patients with a characteristic neuroradiological phenotype of LCC in the absence of mutations in *CTC1*. This purely neurological disorder may present at any age from infancy to adulthood. Our clinical and mutation data allow us to distinguish LCC from Coats plus, leading us to suggest that the use of the "umbrella" term of CRMCC is no longer helpful. Further delineation of the genetic basis of LCC, and its relationship to Coats plus, must await the results of ongoing genetic studies.

Acknowledgments

We are very grateful to the affected families for their involvement in our research. Y.J.C. acknowledges the Manchester National Institute for Health Research (NIHR) Biomedical Research Centre. This work has received support from the Great Ormond Street Hospital Children's Charity and from the Newlife Foundation.

References

1 Tolmie JL, Browne BH, McGettrick PM, Stephenson JBP. A familial syndrome with coats' reaction retinal angiomas, hair and nail defects and intracranial calcification. Eye (Lond) 1988;2(Pt 3): 297–303
2 Crow YJ, McMenamin J, Haenggeli CA, et al. Coats' plus: a progressive familial syndrome of bilateral Coats' disease, characteristic cerebral calcification, leukoencephalopathy, slow pre- and postnatal linear growth and defects of bone marrow and integument. Neuropediatrics 2004;35(1):10–19
3 Briggs TA, Abdel-Salam GMH, Balicki M, et al. Cerebroretinal microangiopathy with calcifications and cysts (CRMCC). Am J Med Genet A 2008;146A(2):182–190
4 Labrune P, Lacroix C, Goutières F, et al. Extensive brain calcifications, leukodystrophy, and formation of parenchymal cysts: a new progressive disorder due to diffuse cerebral microangiopathy. Neurology 1996;46(5):1297–1301
5 Nagae-Poetscher LM, Bibat G, Philippart M, et al. Leukoencephalopathy, cerebral calcifications, and cysts: new observations. Neurology 2004;62(7):1206–1209
6 Linnankivi T, Valanne L, Paetau A, et al. Cerebroretinal microangiopathy with calcifications and cysts. Neurology 2006;67(8): 1437–1443
7 Anderson BH, Kasher PR, Mayer J, et al. Mutations in CTC1, encoding conserved telomere maintenance component 1, cause Coats plus. Nat Genet 2012;44(3):338–342
8 Polvi A, Linnankivi T, Kivelä T, et al. Mutations in CTC1, encoding the CTS telomere maintenance complex component 1, cause cerebroretinal microangiopathy with calcifications and cysts. Am J Hum Genet 2012;90(3):540–549
9 Livingston JH, Stivaros S, van der Knaap MS, Crow YJ. Recognizable phenotypes associated with intracranial calcification. Dev Med Child Neurol 2013;55(1):46–57
10 Brenner C, Del Negro MC, Borigato EMV, Miranda RV. Leukoencephalopathy with cerebral calcifications and cysts. Neurology 2006; 66(9):E32
11 Marelli C, Savoiardo M, Fini N, et al. Late presentation of leucoencephalopathy with calcifications and cysts: report of two cases. J Neurol Neurosurg Psychiatry 2008;79(11):1303–1304
12 Osman NI, Lorincz MT, Hulsing KL, Gebarski SS. Leukoencephalopathy, cerebral calcifications, and cysts: case report. Clin Neurol Neurosurg 2012;114(6):806–809
13 Berry-Candelario J, Kasper E, Eskandar E, Chen CC. Neurosurgical management of leukoencephalopathy, cerebral calcifications, and cysts: A case report and review of literature. Surg Neurol Int 2011; 2:160–164
14 Ummer K, Salam KA, Noone ML, Pradeep Kumar VG, Mampilly N, Sivakumar S. Leukoencephalopathy with intracranial calcifications and cysts in an adult: Case report and review of literature. Ann Indian Acad Neurol 2010;13(4):299–301
15 Gulati A, Singh P, Ramanathan S, Khandelwal N. A case of leukoencephalopathy, cerebral calcifications and cysts. Ann Indian Acad Neurol 2011;14(4):310–312
16 Daglioglu E, Ergungor F, Hatipoglu HG, et al. Cerebral leukoencephalopathy with calcifications and cysts operated for signs of increased intracranial pressure: case report. Surg Neurol 2009; 72(2):177–181
17 Armstrong MJ, Hacein-Bey L, Brown H. Cerebroretinal microangiopathy with calcifications and cysts: demonstration of radiological progression. J Comput Assist Tomogr 2009;33(4):571–572
18 Corboy JR, Gault J, Kleinschmidt-DeMasters BK. An adult case of leukoencephalopathy with intracranial calcifications and cysts. Neurology 2006;67(10):1890–1892
19 Kaffenberger T, Valko PO, von Meyenburg J, et al. A case of late onset leukoencephalopathy with cerebral calcifications and cysts in a 59-year-old woman. Eur J Neurol 2009;16(2):278–281
20 Wargon I, Lacour MC, Adams D, Denier C. A small deep infarct revealing leukoencephalopathy, calcifications and cysts in an adult patient. J Neurol Neurosurg Psychiatry 2008;79(2): 224–225
21 Sener U, Zorlu Y, Men S, Bayol U, Zanapalioglu U. Leukoencephalopathy, cerebral calcifications, and cysts. AJNR Am J Neuroradiol 2006;27(1):200–203